REMARKS

Following entry of the foregoing amendments, claims 5-7 and 11-18 and 20-21 constitute the pending claims in the present application. Applicants have cancelled claim 19. The Examiner has withdrawn claims 20 and 21 as allegedly being drawn to a non-elected invention. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

1. Election/Restrictions

Applicants acknowledge that the set of species has been expanded to the "guest" molecules set forth in claim 11 with a generic therapeutic agent. However, the Examiner has withdrawn claims 20 and 21 from consideration as allegedly being drawn to a non-elected invention. Applicants respectfully disagree and note that these claims were not withdrawn in the Office Action of September 10, 2003, which followed Applicants' June 20, 2003 reply to the Restriction Requirement of May 20, 2003. It is not apparent from the subject matter of the claims why claims 20 and 21 have been withdrawn. Accordingly, Applicants have not designated these claims as withdrawn. Clarification is respectfully requested. In addition, the Examiner is respectfully reminded that upon allowance of a generic claim, withdrawn claims properly dependent on the generic claim must be reinstated and considered. MPEP 809.

2. Claim Objections

Claim 19 is objected to under 37 CFR 1.75(c), as allegedly being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicants respectfully disagree that claim 19 fails to further limit the subject matter of a previous claim. However, solely for the purpose of expediting prosecution, Applicants have cancelled claim 19. Applicants reserve the right to prosecute claims of similar or differing scope to claim 19 in subsequent applications.

3. Claim Rejections – 35 USC 103

Claims 5-7 and 11-19 are rejected under 35 USC 103(a) as allegedly being unpatentable over Zhao et al. (US 6,667,293) in combination with Gonzalez et al. (*Bioconjugate Chem.* **1999**, *10*, 1068-1074). Applicants respectfully traverse the rejection.

Claim 5 is directed to a composition comprising a cyclodextrin-containing polymer and a therapeutic agent and a complexing agent comprising at least one functional group and at least one host/guest moiety that forms an inclusion complex with a host/guest moiety of said polymer, wherein the polymer, the therapeutic agent, and the complexing agent are separate molecules. Claims 6-7 and 11-18 depend directly or indirectly from claim 5.

The Examiner has noted that Zhao discloses the administration of a composition comprising an adamantane-linked oligonucleotide and a cyclodextrin for the treatment of pathogenic infections. Zhao also discloses additional components, such as carriers, diluents, fillers, salts, buffers, stabilizers, solubilizers, in addition to other nucleotides and chemotherapeutic drugs. The reference does not teach a cyclodextrin-containing polymer. The Examiner has also noted that Gonzalez discloses the use of linear, cationic cyclodextrin polymers for the delivery of macromolecular therapeutics, such as oligonucleotides. The Examiner alleges that it would have been obvious to one of ordinary skill in the art at the time the instant invention was filed to modify the compositions of Zhao by the use of cyclodextrin-containing polymers taught by Gonzalez.

Applicants disagree and note that pursuant to MPEP 2142:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicants' disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Applicants assert that there was no motivation or suggestion for one of ordinary skill in the art to combine the teachings of Zhao with those of Gonzalez. Zhao discloses a method that is successful in its ability to reduce the immunostimulatory response caused by a phosphorothioate

oligonucleotide by using at least one cyclodextrin. No shortcomings or disadvantages to the method are taught or suggested. Accordingly, Zhao does not teach or suggest the desirability of modifying the method disclosed therein with the cyclodextrin polymer of Gonzalez. "The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification." See *In re Gordon*, 733 F.2d 900, 902, 221 U.S.P.Q 1125, 1127 (Fed. Cir 1984). Hence, one of ordinary skill in the art would *not be motivated* to modify the successful method of Zhao with the linear, cationic cyclodextrin polymer of Gonzalez since modification with the latter would not obviously produce equal or superior results to the successful Zhao method and since the modification would not correct any disclosed problems with the Zhao method.

Furthermore, Zhao discloses a composition in which a "phosphorothioate oligonucleotide can be covalently linked to an adamantane molecule which is then non-covalently linked to the cyclodextrin" (column 6, lines 63-66) and in which the oligonucleotide linked to the adamantane provides a therapeutic effect (column 7, line 25-26). Also, according to the Zhao method, "at least one cyclodextrin is used to reduce an immunostimulatory response induced by a phosphorothioate oligonucleotide or a protein" (column 3, line 65 to column 4, line 1), and the adamantane moiety and the cyclodextrin of Zhao enter into a host-guest relationship (column 6, line 66 to column 7, line 1) in order to present the oligonucleotide therapeutic and immunostimulatory response-reducing cyclodextrin *together*. Zhao teaches that in order for the cyclodextrin to reduce the immunostimulatory response caused by a phosphorothioate oligonucleotide, the cyclodextrin must be present, since "in the absence of at least one cyclodextrin, the phosphorothioate oligonucleotide or protein induces an immunostimulatory response" (column 4, lines 1-3).

However, the Gonzalez trafficking studies with plasmids employ fluorescently labeled DNA (page 1072, last paragraph). This assay reveals the location and amount only of the DNA, not of the linear, cationic cyclodextrin polymer. As such, Gonzalez concludes that the fluorescently labeled DNA-polymer complex is successful at transfecting cells, but does not determine whether the linear, cationic cyclodextrin polymer is associated with the DNA after entry into the cell, an apparently necessary condition to achieve the advantages sought by Zhao. In fact, Gonzalez does not demonstrate that the linear, cationic cyclodextrin polymer even enters

the cell. One of ordinary skill in the art having read Zhao in light of Gonzalez, would *not be motivated* to modify the method of Zhao to include the linear, cationic cyclodextrin polymer of Gonzalez since there are no teachings in Gonzalez that suggest that the linear, cationic cyclodextrin polymer of Gonzalez would remain associated with the phosphorothioate oligonucleotide of Zhao to achieve a reduction in the immunostimulatory response caused by the phosphorothioate oligonucleotide. One of ordinary skill in the art also would not be motivated to alter the successful Zhao method with a potentially futile modification when there are no perceived benefits of such a modification.

Applicants also assert that one of ordinary skill in the art would *not have a reasonable expectation of success* in combining the method of Zhao with the linear, cationic cyclodextrin polymer of Gonzalez, since the latter is silent on the key association of oligonucleotide therapeutic and immunostimulatory response reducing cyclodextrin and since one of ordinary skill in the art would recognize that, in general, the bioavailability of a compound, such as a sugar, an amino acid, or a cyclodextrin, decreases in progressing from monomer to oligomer to polymer.

Moreover, in Gonzalez, *nowhere* are the disclosed linear, cationic cyclodextrin polymers taught or suggested to enter into a host-guest relationship. Although it is mentioned that cyclodextrin *monomers* can generally form host-guest complexes (page 1068, 2nd column, 1st paragraph), this feature is never attributed to the linear, cationic cyclodextrin polymers that are disclosed therein. Gonzalez teaches that the ability of the disclosed linear, cationic cyclodextrin polymers to bind to DNA and to deliver them to cells is a result of the *cationic* property of the linear, cationic cyclodextrin polymers: "The cationic nature of **4** allows for complexation to DNA" (page 1072, 2nd column, 2nd full paragraph). In fact, Gonzalez discusses at length the importance of the cationic feature of the polymer and its implications on charge ratios between the polymers and the DNA (page 1072, 2nd column, all of 3rd and 4th full paragraphs; see also figures 4-6). Host-guest complexation is not mentioned in Gonzalez as a reason for any beneficial properties of the linear, cationic cyclodextrin polymers. Indeed, the key cationic property of the Gonzalez polymer is a feature not of the cyclodextrin moieties, but of the dimethylsuberimidate (DMS) comonomer. One of ordinary skill in the art, having read Zhao and Gonzalez, would not have been assured of the availability of the polymer to participate in the

host-guest interactions necessary to achieve the advantages sought by Zhao. As such, one of ordinary skill in the art would *not have been motivated* to modify the method of Zhao with the linear, cationic cyclodextrin polymer teachings of Gonzalez, especially in light of the fact that the disclosures reveal no expected improvements that would result from such a modification.

Successful host/guest complexation depends on numerous variables such as host/guest compatibility and sizes of binding energies, variables which can vary between polymers and their corresponding monomers. Since it is well known to one of ordinary skill in the art that it is uncertain whether a given polymer or copolymer will have properties similar to the individual monomers, and since there is no evidence in Gonzalez that cyclodextrin *polymers* can form host-guest complexes, one of ordinary skill in the art could not have had a reasonable expectation that linear, cationic cyclodextrin polymers are capable of forming host-guest complexes simply because it is possible for cyclodextrin monomers. Analogously, just because the cyclodextrin monomers of Zhao have been shown to reduce immunostimulatory response induced by phosphorothioate oligonucleotides, a corresponding cyclodextrin polymer or copolymer cannot also be expected to possess this property. Hence, one of ordinary skill in the art would *not have had a reasonable expectation* that the method of Zhao performed using the linear, cationic cyclodextrin polymers of Gonzalez, would access the necessary properties (immunostimulatory response reduction, host/guest complexation) of the monomer. It is the *present inventors* who have determined that the cyclodextrin moieties in such polymers in fact engage in the formation of inclusion complexes.

Pursuant to MPEP 2141.02, the Examiner is respectfully requested to consider the invention as a whole and to note that "in determining the differences between the prior art and the claims, the question under 35 USC 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious." *See Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d at 1383, 231 U.S.P.Q at 93:

> Focusing on the obviousness of substitutions and differences instead of on the invention as a whole, as the district court did in frequently describing the claimed invention as the mere substitution of monoclonal for polyclonal antibodies in a

> sandwich assay, was a legally improper way to simplify the difficult determination of obviousness.

Indeed, Applicants assert that the substitution of a monomer with the corresponding polymer, as in the modification of the method of Zhao with the polymer of Gonzalez, does not consider the invention as a whole. Since it is well established that a compound and its properties are inseparable (*See In re Papesch*, 315 F.2d 381, 137 U.S.P.Q. 43 (C.C.P.A 1963)), substitution of a monomer for its corresponding polymer is unobvious because each can have different properties from the other.

Furthermore,

> The "as a whole" instruction in title 35 prevents evaluation of the invention part by part...This form of hindsight reasoning, using the invention as a roadmap to find its prior art components, would discount the value of combing various existing features or principles in a new way to achieve a new result – often the very definition of invention.

(*Ruiz v. A.B Chance Co.*, 357 F.3d 1270, 1275 (Fed. Cir. 2004)). Although one, with the aid of hindsight, may conclude that linear cyclodextrin polymers possess the cyclodextrin monomer's properties of immunostimulatory response reduction and/or host-guest complexation, Applicants submit that the relevant case law makes clear that such assumptions may not be made in the determination of the obviousness of an invention over prior art references. Instead, it is *Applicants* who have demonstrated in the instant disclosure that linear cyclodextrin polymers do possess the property of host-guest complexation. Thus, Applicants maintain that one of ordinary skill in the art having read Zhao in light of Gonzalez, would not, without the aid of hindsight, be motivated to modify the method of Zhao to include the linear, cationic cyclodextrin polymer of Gonzalez, and would not expect that such a combination could successfully be utilized, since one of ordinary skill in the art could not reasonably expect the properties of the Zhao cyclodextrin monomer to be retained by the Gonzalez polymer.

Applicants assert for the reasons cited above that the instant invention is not obvious over Zhao or Gonzalez taken separately or in combination. Withdrawal of the rejection is respectfully requested.

Claims 5-7 and 11-19 are rejected under 35 USC 103(a) as allegedly being unpatentable over Zhao et al. (US 6,667,293) in combination with Gonzalez et al. (*Bioconjugate Chem.* **1999**, *10*, 1068-1074) in further combination with Amiel et al (*J. Polym. Anal. Char.*, **1995**) and Carpenter et al (US 4,877,778). Applicants respectfully traverse the rejection.

The Office Action asserts that "it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the composition of Zhao and Gonzalez by substituting the adamantane moiety with any appropriate entity known to form a complex with a cyclodextrin with a reasonable expectation of success." Applicants assert that the arguments presented above with respect to Zhao and Gonzalez alone apply equally to this rejection, and that Amiel and Carpenter fail to overcome the deficiencies of Zhao and Gonzalez. Applicants respectfully request withdrawal of the rejection.

4. Double Patenting Rejection

Claims 5-7 and 11-21 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 5-7 and 11-21 of U.S. Patent Application No. 10/021,312. Applicants will submit a terminal disclaimer, if necessary, upon indication of allowability.

Applicants, however, would like to bring to the Examiner's attention rejections made in related co-pending US application 10/021,312.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,

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